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(polyethylene adj1 glycol) adj5 (polyvinyl adj1 alcohol) and (424/489).ccls.	46

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Search History

DATE: Wednesday, July 06, 2005 Printable Copy Create Case

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L6	(polyethylene adj1 glycol) adj5 (polyvinyl adj1 alcohol) and 424/489.ccls.	46	L6
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L3	L2 and oral$	55	L3
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L1	(polyethylene adj1 glycol) adj3 (polyvinyl adj1 alcohol)	1469	L1

END OF SEARCH HISTORY

L4: Entry 30 of 35 File: USPT Feb 16, 1999

DOCUMENT-IDENTIFIER: US 5872104 A
** See image for Certificate of Correction **
TITLE: Combinations and methods for reducing antimicrobial resistance

Brief Summary Text (18):
An "effective amount of an antimicrobial agent or antibiotic" means an amount, or dose, within the range normally given or prescribed. Such ranges are well established in routine clinical practice and will thus be known to those of skill in the art. Appropriate oral and parenteral doses and treatment regimens are further detailed herein in Table 4 and Table 5. Supplementary information relating specifically to MLS antibiotics is also given in Example I and in Tables 6 and 7, which particularly concern erythromycin, lincomycin, clarithromycin and azithromycin. As this invention provides for enhanced microbial and/or bacterial killing, it will be appreciated that effective amounts of an antimicrobial agent or antibiotic may be used that are lower than the standard doses previously recommended when the antimicrobial or antibiotic is combined with a methylation inhibitor.

Brief Summary Text (22):
The ID.sub.50 /IC.sub.50 ratio required for safe use of the proposed inhibitor-antimicrobial agent combinations will be assessed by determining the ID.sub.50 (median lethal toxic dosage) and the IC.sub.50 (median effective therapeutic dosage) in experimental animals. The optimal dose for human subjects is then defined by fine-tuning the range in clinical trials. In the case of ID.sub.50, the inhibitor is usually administered to mice or rats (orally or intraperitoneal) at several doses (usually 4-5) in the lethal rage. The dose in mg/kg is plotted against % mortality and the dose at 50% represents the ID.sub.50 (Klaassen, 1990). The IC.sub.50 is determined in a similar fashion as described by Cleeland & Squires (1991).

Brief Summary Text (23):
In a clinical trial, the therapeutic dose would be determined by maximizing the benefit to the patient, whilst minimizing any side-effects or associated toxicities. Throughout the detailed examples, various therapeutic ranges are listed. Unless otherwise stated, these ranges refer to the amount of an agent to be administered orally.

Brief Summary Text (48):
The invention also provides novel compositions that contain a combination of antimicrobials and second agents, not previously proposed for combined use, dispersed in a pharmacologically acceptable formulation. The antimicrobial agents and inhibitory second agents may be formulated and administered in any pharmacologically acceptable vehicle, such as parenteral, topical, liposomal, nasal or ophthalmic preparations, with formulations designed for oral administration being currently preferred due to their ease of use.

Detailed Description Text (53):
Antibiotics such as erythromycin, clindamycin, azithromycin, clarithromycin, vancomycin and the like, may be used clinically at a range of doses. Depending on the circumstances, antimicrobial agents may be employed in oral or parenteral

treatment regimens. Appropriate doses are well known to those of skill in the art and are described in various publications, such as (Reese & Betts, 1993; incorporated herein by reference). Table 4 and Table 5 (taken from Reese & Betts, 1993) are included herein to provide ready reference to the currently recommended doses of a variety of antimicrobial agents.

Detailed Description Text (87):
In analyzing the amount of drug to be administered during animal tests, the maximum tolerated dose of a substance should be determined (using the most suitable route of administration). Before use in the treatment of infected animals, the maximum tolerated dose is determined by administering single injections of the substance to groups of animals by the oral, subcutaneous, or intraperitoneal routes. The animals are then observed for survival for periods of 24 hours to 7 days. Such acute toxicity studies establish for each route the 100% toxic dose (LD.sub.100), the 50% lethal does (LD.sub.50), and the maximum tolerated dose (LD.sub.0) at which all animals survive. Experience has allowed the formulation of the rule that approximately 1/5 of the maximum tolerated dose of a substance will be tolerated when treatments are given once daily for 5 days or longer. For 1 to 3 days of treatment, 1/2 the maximum dose can usually be given.

Detailed Description Text (88):
In addition to obtaining initial information on toxicity, some information on absorbability may also be obtained. For example, if a substance is tolerated at 1000 mg/kg when given orally, but toxic when given at a dose of 50 mg/kg intraperitoneally or intravenously, the lack of toxicity by the oral route probably reflects poor oral absorption.

Detailed Description Text (92):
Screening models involve simple one-step infections, simple techniques and schedules of treatment, short-duration experiments, reproducible courses of infection, simple evaluation (all-or-nothing models), economy of test drugs, and low costs. These requirements are best met by the mouse protection test, which is the most widely used in vivo screening model in antibacterial research. The mouse protection test is suitable for determining efficacy and toxicity of new antibacterials and it can indicate whether a drug or new combination is likely to be active orally or parenterally. The manner of conducting such tests will be well known to those of skill in the art in light of the present disclosure and the guidelines set forth below.

Detailed Description Text (95):
In preparing a new agent for testing, the stability, degree of solubility and/or the means by which a uniform suspension may be prepared should be considered. If the antibacterial is insoluble and is to be administered by the oral route, it will generally be prepared in a solution containing 1% carboxymethylcellulose. If an insoluble agent or combination is to be administered by the subcutaneous or intraperitoneal route, a suspension in water is prepared by sonication or homogenization. If these methods fail to produce a uniform suspension, the material is dissolved in DMSO or ethanol. The resulting solution is then diluted to a final concentration of less than 10% DMSO or ethanol, since higher concentrations of these solvents are lethal to mice. For treatment, antibacterials should be freshly prepared each day.

Detailed Description Text (96):
In order to obtain reproducible infections, it is necessary to determine the degree of virulence of each strain to be studied. The lowest dilution of the organisms at which all the animals die is defined as the minimum lethal dose (MLD). Alternatively, in place of MLD one can use multiples of the challenge dose of organisms that kills 50% of the animals (LD.sub.50). After the animals are infected and treated, they are observed over a fixed period and the number of survivors is recorded. The 50% protective dose (PD.sub.50) is calculated in mg/kg. The 50%

protective dose is the same as the 50% curative dose (CD.sub.50) or 50% effective dose (ED.sub.50). By altering the treatment route or schedule, differences in activity can be demonstrated. In addition, the relative efficacy of oral and subcutaneous administration of a substance can be compared.

Detailed Description Text (98):
Many agents that are not active against systemic infections are active against local infections when applied at the site of injection. Different techniques for producing local infections have been described, with the basic principle being the induction of a localized infection that is treated by application of the desired agent to the infected site. Antibiotics and combinations known to be inactive when given orally or subcutaneously have been shown to be active when infiltrated into the site of local infection, as exemplified by the activity of mycin against gram-positive organisms and two gram negative strains (Grunberg et al., 1967).

Detailed Description Text (125):
As a reference point, it is important to note that erythromycin, as an example of an MLS antibiotic, is used clinically at an oral dose of 2000 mg/day (Reese & Betts, 1993). In vitro, in an agar disc susceptibility test, a MIC.sub.90 (minimum inhibitory concentration for 90% inhibition) of about 4 .mu.g/ml for S. aureus is typically determined, while the MIC in broth culture for the same organism is typically between 0.12 and 0.5 .mu.g/ml (Weideman & Atkinson, 1991).

Detailed Description Text (130):
Yebra et al. (1991) showed that SAH (100 .mu.M) and sinefungin (50 .mu.M) inhibit RNA methyltransferase from Streptomyces antibioticus by 97 and 96% respectively. From these results, the inventors estimated that SAH dosage ranges similar to that of sinefungin could be used clinically. Due to the membrane transport characteristics of SAH it is anticipated that the most advantageous method of SAH delivery will be as a liposome or nano particle (Couvreur et al., 1991; Example XIII). Since the net effect of SAHH inhibition is to raise the SAH concentration which causes the inhibition of transmethylation reactions, it is expected that SAH will be used alone or in combination with other methylation inhibitors. Doses useful in therapy with antibiotics, will be from about 1 mg/kg/day to about 100 mg/kg body weight/day, and preferably, from about 5 to about 50 mg/kg body weight/day.

Detailed Description Text (219):
Ara A (0.039M) and 2'-deoxyadenosine (0.183M) were evaluated by the inventors using the first disc susceptibility test:, and shown to enhance the relative erythromycin activity against the resistant S. aureus 27660 by 193 and 233% respectively (Table 8). The proposed dosages for Ara-A and 2'-deoxyadenosine clinical use range between about 1-300 mg/kg/day, and preferably, between about 1-100 mg/kg/day. LD.sub.50 of Ara-A in mice is 4,677 mg/kg (i.p) and 7,950 mg/kg orally (Windholz et al., 1983).

Detailed Description Text (300):
It has been shown in clinical trials that DFMO is effective against Trypanosomiasis at different dosage levels and modes of treatment by different groups. As an example, DFMO was administered in one study at 400 mg/kg qid, for 4 to 6 weeks. In another study, DFMO was administered 20 g i.v. for 11 days, 30 g daily for 2 days and 15 g orally every day for 7 weeks. Tyms (1988) concluded that DFMO is safe and well tolerated and the side effects are reversible. Additionally, DL-.alpha.-monofluoromethyldehydroornithine methylester, a DFMO analogue, is take up more readily than DFMO (K.sub.i =39 .mu.M) and readily cleaved to the free amino acid within the cell and has a K.sub.i of 3 .mu.M.

Detailed Description Text (313):
5-Azacitidine inhibits the maturation of rRNA (Suhudolnik, 1979). The formation of 28S and 18S, but not of 38S RNA, is severely inhibited. 5-Azacitidine is commercially available from Sigma Chemical Company. The structure of 5-Azacitidine

is shown below. Budavari et al. (1989) reported the oral toxicity of 5-azacitidine as 572.3 mg/kg in mice. This compound is therefore proposed for use with antibiotics at doses of between about 1 and about 300 mg/kg body weight/day, and preferably, between about 10 and about 75 mg/kg body weight/day. ##STR19## 2. Cordycepin (3'-deoxyadenosine)

Detailed Description Text (354):
In addition to the compounds formulated for parenteral administration, other pharmaceutically acceptable forms are also contemplated for use, including, e.g., tablets or other solids for oral administration; time release capsules; forms for topical administration, including creams and lotions; mouthwashes; aerosols, inhalents and the like.

Detailed Description Text (356):
2. Oral Formulations

Detailed Description Text (357):
In certain embodiments, active compounds may be administered orally. This is contemplated for agents that are generally resistant, or have been rendered generally resistant, to proteolysis by digestive enzymes. Such compounds are comtemplated to include the antibiotics and most of the inhibitory second agents disclosed herein. Naturally, the preferred inhibitors will be the more active compounds and those already cleared by the FDA for other uses, as will be known to those of skill in the art in light of the present disclosure.

Detailed Description Text (358):
For oral administration, the active compounds and/or combinations thereof may be administered, for example, with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsule, or compressed into tablets, or incorporated directly with the food of the diet. For oral therapeutic administration, the active compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compounds or combinations thereof. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of the unit. The amount of active compounds in such therapeutically useful compositions is such that a suitable dosage will be obtained.

Detailed Description Text (364):
Inhalations and inhalants are pharmaceutical preparations designed for delivering a drug or compound into the respiratory tree of a patient. A vapor or mist is administered and reaches the affected area to give relief from symptoms of bronchial and nasal congestion. Inhalations may be administered by the nasal or oral respiratory routes. The administration of inhalation solutions is only effective if the droplets are sufficiently fine and uniform in size so that the mist reaches the bronchioles.

Detailed Description Text (365):
Another group of products, also known as inhalations, and sometimes called insufflations, consists of finely powdered or liquid drugs that are carried into the respiratory passages by the use of special delivery systems, such as pharmaceutical aerosols, that hold a solution or suspension of the drug in a liquefied gas propellant. When released through a suitable valve and oral adapter, a metered does of the inhalation is propelled into the respiratory tract of the patient.

Detailed Description Text (370):
Suitable preservatives for use in such a solution include benzalkonium chloride, benzethonium chloride, chlorobutanol, thimerosal and the like. Suitable buffers

include boric acid, sodium and potassium bicarbonate, sodium and potassium borates, sodium and potassium carbonate, sodium acetate, sodium biphosphate and the like, in amounts sufficient to maintain the pH between about 6 and 8, and preferably, between about pH 7 and pH 7.5. Suitable tonicity agents are dextran 40, dextran 70, dextrose, glycerin, potassium chloride, propylene glycol, sodium chloride, and the like, such that the sodium chloride equivalent of the ophthalmic solution is in the range 0.9 plus or minus 0.2%. Suitable antioxidants and stabilizers include sodium bisulfite, sodium metabisulfite, sodium thiosulfate, thiourea and the like. Suitable wetting and clarifying agents include polysorbate 80, polysorbate 20, poloxamer 282 and tyloxapol. Suitable viscosity-increasing agents include dextran 40, dextran 70, gelatin, glycerin, hydroxyethylcellulose, hydroxymethylpropylcellulose, lanolin, methylcellulose, petrolatum, polyethylene glycol, polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose and the like. The ophthalmic preparation will be administered topically to the eye of the subject in need of treatment by conventional methods, for example in the form of drops or by bathing the eye in the ophthalmic solution.

Detailed Description Text (371):
6. Liposomes and Nanoparticles

Detailed Description Text (372):
Couvreur et al. (1991) review the potential of liposomes and nanoparticles in the targeted antibiotic therapy of intracellular bacterial infections and diseases. Nanoparticles can generally entrap antibiotics in a stable and reproducible way (Henry-Michelland et al., 1987). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 .mu.m) should be designed using polymers able to be degraded in vivo. Biodegradable polyalkyl-cyanoacrylate nanoparticles that meet these requirements are proposed for use in the present invention. They are easily made, as described by Couvreur et al. (1984; 1988). In serum, the liberation of ampicillin from nanoparticles was found to follow zero-order kinetics (Fattal et al., 1991a, 1991b).

Detailed Description Text (375):
The formation and use of liposomes is generally known to those of skill in the art. For example, Couvreur et al. (1991; incorporated herein by reference) describe the use of liposomes and nanoparticles in the targeted antibiotic therapy of intracellular bacterial infections and diseases. Recently, liposomes were developed with improved serum stability and circulation half-times (Gabizon & Papahadjopoulos, 1988; Allen & Choun, 1987).

Detailed Description Text (383):
Using the combined antimicrobial formulations described herein in liposomal formulations will lead to further particular advantages that relate to targeting. The properties of liposomes and nanoparticles will likely improve therapy in a number of bacterial infections that are presently difficult to cure. As set forth by Couvreur et al. (1991), liposomes and nanoparticles themselves cannot escape from the circulation because of the endothelial barrier, with exception to tissues with discontinuous endothelia lining their capillaries (i.e., liver, spleen, and bone marrow). This leads to the rapid clearance of these ultrafine particulate carriers from the blood and to their capture by the cells of the reticuloendothelial system (Poste, 1933; Grislain et al., 1983). This corresponds exactly to the sane tissue distribution pattern as that of the majority of the bacteria responsible for intracellular infection. In addition, it has been shown that liposomes are taken up by circulating blood monocytes, which are known to infiltrate some infectious lesions (Tulkens, 1985). Also, as with bacteria, both liposomes and nanoparticles will likely penetrate cells by endocytosis, first forming phagosomes, which in turn fuse with lysosomes to form phagolysosomes or secondary lysosomes (Couvreur et al., 1977).

Detailed Description Text (384):

The advantages of liposomes and nanoparticles has been described for various cases. Liposome-associated cephalothin has been shown to be more effective than free drug in the treatment of experimental murine salmonellosis (Desiderio and Campbell, 1933). The therapeutic index of ampicillin, calculated on the basis of mouse mortality, has been reported to be increased by 120-fold upon binding to nanoparticles (Fattal et al., 1989). Guinea pigs infected by Brucella canis and treated with liposome-entrapped streptomycin were found to be free of bacteria (2.times.10 mg/kg), whereas animals treated with the free drug, for the same schedule of administration, showed only a minor reduction in the number of surviving bacteria (Fountain et al., 1985). The delivery of antibacterial drugs to phagocytic cells has also been demonstrated to be feasible with amikacin (Duzgunes et al., 1988), kanamycin and tobramycin (Fountain et al., 1985).

Detailed Description Paragraph Table (2):

TABLE 2

ANTIBIOTICS OF CHOICE FOR COMMON PATHOGENS Pathogen Antibiotic of First Choice.sup.a Alternative Agent.sup.a

Gram-positive cocci Staphylococcus aureus or S. epidermidis Non-penicillinase-Penicillin A first-generation cephalosporin, producing vancomycin, imipenem, or clindamycin; a fluoroquinolone.sup.b Penicillinase- Penicillinase-resistant A first-generation cephalosporin, producing penicillin (e.g., vancomycin, clindamycin, imipenem, oxacillin or nafcillin) amoxicillin-clavulanic acid, ticarcillin-clavulanic acid, ampicillin-sulbactam; a fluoroquinolone.sup.b Methicillin-resistant Vancomycin with or without TMP-SMZ, minocycline gentamicin and/or rifampin Streptococci Group A, C, G Penicillin A cephalosporin.sup.a, vancomycin, erythromycin; clarithromycin; azithromycin; clindamycin Group B Penicillin (or ampicillin) A cephalosporin.sup.a, vancomycin, or erythromycin Enterococcus Endocarditis or Penicillin (or ampicillin) Vancomycin with gentamicin other serious with gentamicin infection Uncomplicated Ampicillin or amoxicillin A fluoroquinolone, nitrofurantoin urinary tract infection Viridans group Penicillin G (with or A cephalosporin.sup.a, vancomycin without gentamicin) S. bovis Penicillin G A cephalosporin.sup.a, vancomycin S. pneumoniae Penicillin G A cephalosporin.sup.a, erythromycin, chloramphenicol, vancomycin Gram-negative cocci Neisseria gonorrhoeae Ceftriaxone Spectinomycin, a fluoroquinolone, cefoxitin, cefixime, cefotaxime (see Appendix E) N. meningitidis Penicillin G Third-generation cephalosporin, chloramphenicol Moraxella TMP-SMZ Amoxicillin-clavulanic acid; an (Branhamella) erythromycin; clarithromycin catarrhalis azithromycin, cefuroxime, cefixime, third-generation cephalosporin, tetracycline Gram-positive bacilli Clostridium perfringens Penicillin G Chloramphenicol, metronidazole, or (and Clostridium sp.) clindamycin Listeria monocytogenes Ampicillin with or without TMP-SMZ gentamicin Gram-negative bacilli Acinetobacter Imipenem Tobramycin, gentamicin, or amikacin, usually with ticarcillin or piperacillin (or similar agent); TMP-SMZ Aeromonas hydrophila TMP-SMZ Gentamicin, tobramycin; imipenem; a fluoroquinolone Bacteroides Bacteroides sp. Penicillin G Clindamycin, cefoxitin, (oropharyngeal) metronidazole, chloramphenicol, cefotetan, ampicillin-sulbactam B. fragilis strains Metronidazole Clindamycin; ampicillin-sulbactam; (gastrointestinal imipenem; cefoxitin.sup.c ; cefotetan.sup.c ; strains) ticarcillin-clavulanic acid; piperacillin.sup.c; chloramphenicol; cefmetazole.sup.c Campylobacter fetus, A fluoroquinolone (adults) A tetracycline, gentamicin jejuni or an erythromycin Enterobacter sp. Imipenem An aminoglycoside and piperacillin or ticarcillin or mezlocillin; a third-generation cephalosporin.sup.d ; TMP-SMZ; aztreonam; a fluoroquinolone Escherichia coli Uncomplicated urinary TMP-SMZ A cephalosporin or a fluoroquinolone tract infection Recurrent or systemic A cephalosporin.sup.c Ampicillin with or without an infection aminoglycoside, TMP-SMZ, oral fluoroquinolones useful in recurrent infections, ampicillin- sulbactam, ticarcillin-clavulanic acid, aztreonam Haemophilus influenzae (coccobacillary) Life-threatening Cefotaxime or ceftriaxone Chloramphenicol; cefuroxime for infections pneumonia) Upper respiratory TMP-SMZ Ampicillin or amoxicillin; infections and cefuroxime; a sulfonamide with or bronchitis without an

erythromycin; cefuroxime-axetil; third-generation cephalosporin, amoxicillin-clavulanic acid, cefaclor, tetracycline; clarithromycin; azithromycin Klebsiella pneumoniae A cephalosporin.sup.c An aminoglycoside, imipenem, TMP- SMZ, ticarcillin-clavulanic acid, ampicillin-sulbactam, aztreonam, a fluoroquinolone; amoxicillin- clavulanic acid Legionella spp. Erythromycin with rifampin TMP-SMZ; clarithromycin; azithromycin; ciprofloxacin Pasteurella multocida Penicillin G Tetracycline, cefuroxime, amoxicillin-clavulanic acid, ampicillin-sulbactam Proteus sp. Cefotaxime, ceftizoxime, or An aminoglycoside; ticarcillin or ceftriaxone.sup.f piperacillin or mezlocillin; TMP- SMZ; amoxicillin-clavulanic acid; ticarcillin-clavulanic acid, ampicillin-sulbactam; a fluoroquinolone; aztreonam; imipenem Providencia stuartii Cefotaxime, ceftizoxime, or Imipenem; an aminoglycoside often ceftriaxone.sup.f combined with ticarcillin or piperacillin or similar agent; ticarcillin-clavulanic acid; TMP- SMZ, a fluoroquinolone; aztreonam Pseudomonas aeruginosa Gentamicin or tobramycin or An aminoglycoside and ceftazidime; (nonurinary tract amikacin (combined with imipenem, or aztreonam plus an infection) ticarcillin, aminoglycoside; ciprofloxacin piperacillin, etc. for serious infections) (urinary tract Ciprofloxacin Carbenicillin; ticarcillin, infections) piperacillin, or mezlocillin; ceftazidime; imipenem; aztreonam; an aminoglycoside Pseudomonas cepacia TMP-SMZ Ceftazidime, chloramphenicol Salmonella typbi Ceftriaxone Ampicillin, amoxicillin, TMP-SMZ, chloramphenicol; a fluoroquinolone Other species Cefotaxime or ceftriaxone Ampicillin or amoxicillin, TMP-SMZ, chloramphenicol; a fluoroquinolone Serratia Cefotaxime, ceftizoxime, or Gentamicin or amikacin; imipenem; ceftriaxone.sup.f TMP-SMZ; ticarcillin, piperacillin, or mezlocillin; aztreonam; a fluoroquinolone Shigella A fluoroquinolone TMP-SMZ; ceftriaxone; ampicillin Vibrio cholerae A tetracycline TMP-SMZ; a fluoroquinolone (chlorea) Vibrio vulnificus A tetracycline Cefotaxime Xanthomonas TMP-SMZ Minocycline, ceftazidime, a (Pseudomonas) fluoroquinolone maltophilia Yersinia enterocolitica TMP-SMZ A fluoroquinolone; an aminoglycoside; cefotaxime or ceftizoxime Yersinia pestis (plague) Streptomycin A tetracycline; chloramphenicol; gentamicin

Key: TMPSMZ = trimethoprimsulfamethoxazole. .sup.a Choice presumes susceptibility studies indicate that the pathogen is susceptible to the agent. .sup.b The experience with fluoroquinolone use in staphylococcal infections is relatively limited. The fluoroquinolones should be used onl in adults. .sup.c Up to 15-20% of strains may be resistant. .sup.d Enterobacter spp. may develop resistance to the cephalosporins. .sup.e Specific choice will depend on susceptibility studies. Thirdgeneration cephalosporins may be exquisitely active against many gramnegative bacilli (e.g., E. coli, Klebsiella sp.). In some geographic areas, 20-25% of communityacquired E. coli infections may be resistant to ampicillin (amoxicillin). .sup.f In severely ill patients, this is often combined with an aminoglycoside while awaiting susceptibility data.

Detailed Description Paragraph Table (4):

TABLE 4 COMMON ANTIBIOTICS AND USUAL ORAL DOSES ANTIBIOTIC DOSAGE Penicillin V 250 mg qid Rugby (generic) V-cillin K Dicloxacillin 250 mg qid Glenlawn (generic) Dynapen Cloxacillin (Tegopen) 250 mg qid Amoxicillin 250 mg tid Rugby (generic) Polymox Ampicillin 250 mg qid Moore (generic) Polycillin Augmentin tid 250-mg tablets chewables (250 mg) 125-mg (suspension) chewables (125 mg) Carbenicillin (Geocillin) 382 mg qid (1 tb) 2 tab qid Cephalexin 250 mg qid Rugby (generic) Keflex Rugby (generic) 500 mg qid Keflex Cefadroxil 1 gm bid Rugby (generic) Duricef Cephradine 250 mg qid Rugby (generic Velosef Rugby (generic) 500 mg qid Velosef Cefaclor 250 mg tid Ceclor Cefuroxime axetil Ceftin 125 mg bid 250 mg bid 500 mg bid Cefixime 400 mg q24h Suprax Cefprozil 250 mg q12h Cefzil Loracarbef (Lorabid) 200 mg bid Cefpodoxime proxetil 200 mg bid (Vantin) Clindamycin 300 mg q8h Cleocin TMP/SMZ 1 double-strength bid Bactrim Septra (generic) Trimethoprim 100 mg bid Rugby (generic) Proloprim Erythromycin (base) 250 mg gid Abbott E-mycin (delayed release) Erythromycin stearate 250 mg qid Rugby (generic) Azithromycin 1 g once only 500 mg, Zithromax day 1, plus 250 mg, day 2-5 Clarithromycin 250 mg bid Biaxin 500 mg bid

Tetracycline hydrochloride 250 mg qid Mylan Sumycin 250 Doxycycline 100 mg qd (with 200-mg Lederle (generic) initial load) Vibramycin Vancomycin Capsules Vancocin HCl (oral soln/powder) 125 mg q6h PO Metronidazole 250 mg qid Rugby (generic) Flagyl Norfloxacin 400 mg bid Noroxin Ciprofloxacin 250 mg bid Cipro 500 mg bid 750 mg bid Ofloxacin 200 mg bid Floxin 300 mg bid 400 mg bid Lomefloxacin Maxaquin 400 mg once qd _____

CLAIMS:

60. The method of claim 9 or 10, wherein said antimicrobial agent and said methylation inhibitor are administered orally.

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L4: Entry 32 of 35 File: USPT Dec 22, 1998

DOCUMENT-IDENTIFIER: US 5851551 A
TITLE: Sustained-release matrices for dental application

Brief Summary Text (3):
Most humans suffer from tooth decay and/or periodontal disease caused by bacteria in the mouth. As a result, decreasing the number of bacteria in the mouth has long been the target of persons working in the health care field. The most common way of minimizing the number of bacteria is to brush and floss the teeth regularly, and to visit a dental hygienist to have the teeth and gums cleaned thoroughly. Another prior approach is oral rinsing, including with a solution containing a known anti-microbial agent like chlorhexidine digluconate.

Brief Summary Text (9):
In one aspect the invention features an oral brush that includes a sustained-release matrix made from a support resin, a water-soluble substance (preferably a water-soluble polymer), and an anti-microbial agent. When the matrix contacts water, the water-soluble substance dissolves, causing the release of the anti-microbial agent.

Brief Summary Text (10):
An oral brush, as used herein, is any brush that includes a handle and a head attached to a brush designed for insertion into the mouth. The brush portion preferably is made from the common bristles found in toothbrushes, but can also be designed for massaging the gums rather than the teeth. For example, Kaminski et al., U.S. Ser. No. 07/724,129, which was filed on Jul. 1, 1991, is assigned to the same assignee as the present application and is hereby incorporated by reference, describes an interdental foam brush in which the brush portion is made of a soft polyurethane foam.

Brief Summary Text (18):
The invention features, in another aspect, an oral brush that includes a template including a water-soluble polymer and an anti-microbial agent.

Brief Summary Text (21):
Another aspect of the invention features a wear-indicator oral brush that includes a matrix containing a colorant (e.g., a dye) and a water-leachable substance that is released from the matrix when the oral brush is used to cause the matrix to change color after repeated (at least 5) typical uses. The preferred matrix is a template that includes two co-extruded or co-molded layers. The outer layer, which contacts water and saliva during brushing, preferably includes the water-leachable substance, which can be, for example, a water-soluble polymer like polyethylene oxide, or the colorant itself, or a combination of the two. The second, inner, layer preferably includes a support resin, and can also include a colorant (e.g., TiO.sub.2) that provides the template with a different color, or shade of color, than the colorant included in the outer layer. The first layer preferably also includes a support resin, although less than the amount included in the second layer, and also can include an anti-microbial agent.

Brief Summary Text (22):
The oral brushes having a matrix including a colorant, i.e., pigment or dye,

provide a means to monitor the degree of wear of the brush. Where the water-leachable substance includes the colorant, over time as the brush is used the colorant is released, causing the matrix to change color. In those embodiments in which the colorant is not water-leachable and thus is not released from the matrix, typically the portion of the template including a water-leachable substance dissolves away through repeated use of the brush to expose the section of the matrix that includes the colorant, providing an indication of wear. The amounts and types of colorant in the matrix can be adjusted so that the color of the matrix changes after the number of uses through which a typical brush should be used. When the colored matrix also includes an anti-microbial agent, the change of colorant can be designed to correspond with the depletion of the agent in the matrix.

Detailed Description Text (61):
The wear-indicator template preferably includes two layers, each with a different colorant. The outer layer includes a water-soluble polymer (preferably polyethylene oxide, polyethylene glycol, or polyvinyl alcohol) and a colorant, preferably a water-leachable colorant; a support resin is optional. The inner layer includes a support resin and a second colorant, like titanium dioxide, which provides a solid white appearance. The different colorants should be selected to provide a clear contrast so that a user can plainly discern the color change as the colorant in the outer layer leaches out over time.

Other Reference Publication (6):
Muller et al., "Camouflage nanospheres: a new approach to bypassing phagocytic blood clearance by surface modified particulate carriers", Pharm. Pharmacol Lett, 3 (1993) 67-70.

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L3: Entry 51 of 55 File: USPT Mar 12, 1996

DOCUMENT-IDENTIFIER: US 5498421 A
TITLE: Composition useful for in vivo delivery of biologics and methods employing same

Brief Summary Text (5):
The size of particles and their mode of delivery determines their biological behavior. Strand et al. [in Microspheres-Biomedical Applications, ed. A. Rembaum, pp 193-227, CRC Press (1988)] have described the fate of particles to be dependent on their size. Particles in the size range of a few nanometers (nm) to 100 nm enter the lymphatic capillaries following interstitial injection, and phagocytosis may occur within the lymph nodes. After intravenous/intraarterial injection, particles less than about 2 microns will be rapidly cleared from the blood stream by the reticuloendothelial system (RES), also known as the mononuclear phagocyte system (MPS). Particles larger than about 7 microns will, after intravenous injection, be trapped in the lung capillaries. After intraarterial injection, particles are trapped in the first capillary bed reached. Inhaled particles are trapped by the alveolar macrophages.

Brief Summary Text (6):
Pharmaceuticals that are water-insoluble or poorly water-soluble and sensitive to acid environments in the stomach cannot be conventionally administered (e.g., by intravenous injection or oral administration). The parenteral administration of such pharmaceuticals has been achieved by emulsification of oil solubilized drug with an aqueous liquid (such as normal saline) in the presence of surfactants or emulsion stabilizers to produce stable microemulsions. These emulsions may be injected intravenously, provided the components of the emulsion are pharmacologically inert. For example, U.S. Pat. No. 4,073,943 describes the administration of water-insoluble pharmacologically active agents dissolved in oils and emulsified with water in the presence of surfactants such as egg phosphatides, pluronics (copolymers of polypropylene glycol and polyethylene glycol), polyglycerol oleate, etc. PCT International Publication No. WO85/00011 describes pharmaceutical microdroplets of an anaesthetic coated with a phospholipid, such as dimyristoyl phosphatidylcholine, having suitable dimensions for intradermal or intravenous injection.

Brief Summary Text (10):
Thus, the poor aqueous solubility of many biologics presents a problem for human administration. Indeed, the delivery of pharmacologically active agents that are inherently insoluble or poorly soluble in aqueous medium can be seriously impaired if oral delivery is not effective. Accordingly, currently used formulations for the delivery of pharmacologically active agents that are inherently insoluble or poorly soluble in aqueous medium require the addition of agents to solubilize the pharmacologically active agent. Frequently, however, severe allergic reactions are caused by the agents (e.g., emulsifiers) employed to solubilize pharmacologically active agents. Thus, a common regimen of administration involves treatment of the patient with antihistamines and steroids prior to injection of the pharmacologically active agent to reduce the allergic side effects of the agents used to aid in drug delivery.

Brief Summary Text (34):

For example, a suspension of polymeric shells of the invention can be administered intravenously, making imaging of vascularized organs (e.g., liver, spleen, lymph and lung) and bone marrow possible. Organ target specificity is achieved as a result of uptake of the micron-sized organofluorine-containing polymeric shells by the reticuloendothelial system (RES) (also known as the mononuclear phagocyte (MNP) system). Organs such as the liver and spleen play an important role in removing foreign species (e.g., particulate matter) from the bloodstream, and hence are often referred to as the "blood filtering organs". These organs make up a major part of the RES. In addition, lymph nodes within the lymphatic circulation contain cells of the RES. Consequently, imaging of the lymphatic system is possible employing micron-sized organofluorine-containing polymeric shells of the present invention. Given orally or as a suppository, imaging of the stomach and gastrointestinal tract can be carried out. Such suspensions can also be injected into non-vascular space, such as the cerebro-spinal cavity, allowing imaging of such space as well.

Drawing Description Text (2):
FIG. 1 shows a schematic of a polymeric shell prepared in accordance with the present invention. In the Figure, A refers to the insoluble disulfide crosslinked polymeric shell, B refers to the interior of the polymeric shell, which can contain oxygen or other gas, a fluorocarbon containing dissolved oxygen, a biocompatible oil having biologic dissolved therein, a water-in-oil emulsion containing biologic dissolved in aqueous media, a suspension of solid particles dispersed in a liquid, and the like, C designates the thickness of the polymeric shell, typically about 5-50 nanometers, and D refers to the diameter of the polymeric shell, typically in the range of about 0.1 up to 20 .mu.m.

Detailed Description Text (11):
As used herein, the term "in vivo delivery" refers to delivery of a biologic by such routes of administration as oral, intravenous, subcutaneous, intraperitoneal, intrathecal, intramuscular, intracranial, inhalational, topical, transdermal, suppository (rectal), pessary (vaginal), and the like.

Detailed Description Text (33):
In addition, the polymeric shell can optionally be modified by a suitable agent, wherein the agent is associated with the polymeric shell through an optional covalent bond. Covalent bonds contemplated for such linkages include ester, ether, urethane, diester, amide, secondary or tertiary amine, phosphate ester, sulfate ester, and the like bonds. Suitable agents contemplated for this optional modification of the polymeric shell include synthetic polymers (polyalkylene glycols (e.g., linear or branched chain polyethylene glycol), polyvinyl alcohol, polyhydroxyethyl methacrylate, polyacrylic acid, polyethyloxazoline, polyacrylamide, polyvinyl pyrrolidinone, and the like), phospholipids (such as phosphatidyl choline (PC), phosphatidyl ethanolamine (PE), phosphatidyl inositol (PI), sphingomyelin, and the like), proteins (such as enzymes, antibodies, and the like), polysaccharides (such as starch, cellulose, dextrans, alginates, chitosan, pectin, hyaluronic acid, and the like), chemical modifying agents (such as pyridoxal 5'-phosphate, derivatives of pyridoxal, dialdehydes, diaspirin esters, and the like), or combinations of any two or more thereof.

Detailed Description Text (43):
In contrast to the invention process, the prior art method of glutaraldehyde crosslinking is nonspecific and essentially reactive with any nucleophilic group present in the protein structure (e.g., amines, sulfhydryls and hydroxyls). Heat denaturation as taught by the prior art significantly and irreversibly alters protein structure. In contrast, disulfide formation contemplated by the present invention is very specific, and does not substantially denature the protein. In addition, particles or droplets of biologic contained within a polymeric shell differ from crosslinked or heat denatured protein microspheres of the prior art because the polymeric shell produced by the invention process is relatively thin

compared to the diameter of the coated particle. It has been determined (by transmission electron microscopy) that the "shell thickness" of the polymeric coat is approximately 25 nanometers for a coated particle having a diameter of 1 micron (1000 nanometers). In contrast, microspheres of the prior art do not have protein shells, but rather, have protein dispersed throughout the volume of the microsphere.

Detailed Description Text (58):
Fluosol-DA (Alpha Therapeutics), an emulsion of perfluorodecalin and perfluorotripropyl amine, is the only FDA approved product for use in the prevention of transient ischemia in balloon coronary angioplasty. Another fluorocarbon product, Oxygent (Alliance Pharmaceuticals), or perfluorooctyl bromide, has approval as an oral imaging agent. For review of perfluoro compounds as blood substitutes, see Riess et al. in Angew Chem. Int. Ed. Engl. 17:621-634 (1978).

Detailed Description Text (108):
Preferred routes for in vivo administration are the intravenous, intraarterial, intramuscular, subcutaneous, intraperitoneal, oral, inhalational, topical, transdermal, suppository, pessary and the like.

Detailed Description Text (171):
Contrast agents of the present invention may be introduced into the body space in various ways depending on the imaging requirements. For example, aqueous liquid suspensions may be placed in the gastrointestinal tract by oral ingestion or suppository (e.g., to obtain images of the stomach and gastrointestinal tract), inserted by syringe into non-vascular spaces such as the cerebro-spinal cavity, or injected into the vascular system generally or into the vessels of a specific organ such as the coronary artery. In addition, contrast agents of the invention can also be injected into other body spaces such as the anterior and posterior eye spaces, the ear, the urinary bladder (e.g., by way of the urethra), the peritoneal cavities, ureter, urethra, renal pelvis, joint spaces of the bone, lymphatic vessels, the subarachnoid spaces, the ventricular cavities, and the like.

Detailed Description Text (233):
Cyclosporine is currently delivered in oral form either as capsules containing a solution of cyclosporine in alcohol, and oils such as corn oil, polyoxyethylated glycerides and the like, or as a solution in olive oil, polyoxyethylated glycerides, and the like. It is also administered by intravenous injection, in which case it is dissolved in a solution of ethanol (approximately 30%) and Cremaphor (polyoxyethylated castor oil) which must be diluted 1:20 to 1:100 in normal saline or 5% dextrose prior to injection. Compared to an intravenous (i.v.) infusion, the absolute bioavailibility of the oral solution is approximately 30% (Sandoz Pharmaceutical Corporation, Publication SDI-Z10 (A4), 1990). In general, the i.v. delivery of cyclosporine suffers from similar problems as the currently practiced i.v. delivery of taxol, i.e., anaphylactic and allergic reactions believed to be due to the Cremaphor, the delivery vehicle employed for the i.v. formulation. In addition, the intravenous delivery of drug (e.g., cyclosporike) encapsulated as described here avoids dangerous peak blood levels immediately following administration of drug. For example, a comparison of currently available formulations for cyclosporine with the above-described encapsulated form of cyclosporine showed a five-fold decrease in peak blood levels of cyclosporine immediately following injection.

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L6: Entry 35 of 46 File: USPT Dec 9, 1997

DOCUMENT-IDENTIFIER: US 5695784 A
TITLE: Flavor-masked pharmaceutical compositions

Detailed Description Text (4):
Binders which can be used to increase the mechanical strength of the microgranules are substances such as acacia gum, alginic acid and alginates, carboxymethylcellulose, ethylcellulose, gelatine, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, xanthan gum, pectin, tragacanth, microcrystalline cellulose, hydroxyethylcellulose, ethylhydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycols, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid, gum arabic, lactose, starch (wheat, maize, potato and rice starch), sucrose, glucose, mannitol, sorbitol, xylitol, stearic acid, hydrogenated cottonseed oil, hydrogenated castor oil, vinylpyrrolidone-vinyl acetate copolymers, fructose, methylhydroxyethylcellulose, agar-agar, carrageenan, karaya gum, chitosan, starch hydrolysates and the like. The use of polyvinylpyrrolidone 25 in a concentration of 1-10%, relative to the microgranules, is particularly advantageous.

Detailed Description Text (11):
These coatings, which are not water-soluble per se, can be combined with water-soluble polymers, which provide for pore formation in the coating, to increase the permeability. Water-soluble pore-forming agents which can be used are substances such as hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, sodium carboxymethylcellulose, dextran, dextrins, cyclodextrins, polyethylene glycols, polyvinyl alcohols, polyvinylpyrrolidones, starch and starch-hydrolysates such as, for example, modified types of starch (gelatinised starch, STA-RX 1 500, Celutab, maltodextrins), sugars and sugar replacements such as mono-, di- and oligosaccharides, sucrose, fructose, lactose, dextrose, mannitol, sorbitol and xylitol and alginic acid and alginates, tragacanth, pectins, gum arabic and gelatin. Preferred pore-forming agents within the meaning of the invention are hydroxypropylcellulose, hydroxypropylmethylcellulose and methylcellulose.

Detailed Description Text (66):
Viscosity-increasing and sedimentation-delaying auxiliaries which can be employed are acacia gum, agar-agar, agarose, alginic acid and alginates, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, sodium carboxymethylcellulose, dextran, polyethylene glycol, polyvinyl alcohol, polyvinylpyrrolidone, starch and xanthan gum. The concentrations of the polymers are between 0.01 and 1.0 g, preferably between 0.1 and 0.8 g per sachet of 5-6 g total weight. It is very important that the viscosity-increasing substance dissolves rapidly in cold water and does not lead to lump formation.

Current US Cross Reference Classification (1):
424/489

L6: Entry 44 of 46 File: USPT Jan 3, 1995

US-PAT-NO: 5378474
DOCUMENT-IDENTIFIER: US 5378474 A

TITLE: Sustained release pharmaceutical composition

DATE-ISSUED: January 3, 1995

INVENTOR-INFORMATION:

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US-CL-CURRENT: 424/469; 424/461, 424/462, 424/468, 424/489, 424/490, 424/493, 424/494, 424/495, 424/497

CLAIMS:

What is claimed is:

1. A sustained release pharmaceutical pellet composition for administration to a patient at a predetermined dosage and interval which comprises: a core element containing a therapeutically effective amount of at least one active ingredient having an aqueous solubility of at least 1 in 30 and a coating on said core element which comprises the following components:

(a) from 1 to 85% by weight of a matrix polymer which is insoluble at a pH of from 1 to 7.5 and contributes to the control of the rate of release of the active ingredient in the stomach and intestines;

(b) from 1 to 30% of an enteric polymer which is substantially insoluble at a pH of from 1 to 4, sufficient to delay the release of the active ingredient in the stomach, but which is soluble at a pH of from 6 to 7.5 so as not to substantially delay release in the intestines;

(c) from 1 to 60% of a compound soluble at a pH of from 1 to 4, sufficient to enable initiation of release of the active ingredient in the stomach; said percentages being by weight based on the total weight of components (a), (b), and (c); the ratio of the components (a), (b), and (c) in said coating being such that a dose of the pellet composition delivers to the patient a therapeutically effective amount of said active ingredient over the course of said predetermined interval, so as to maintain an active ingredient blood level at steady state of at least 75% of maximum blood level for more than approximately 4 hours and so that the time at which the active ingredient reaches its maximum concentration is between about 4 and about 30 hours.

2. The sustained release pharmaceutical pellet composition of claim 1 wherein the time at which the active ingredient reaches its maximum concentration is between about 4 and about 12 hours.

3. The sustained release pharmaceutical pellet composition of claim 1 wherein the active ingredient of high solubility is selected from the group consisting of antihistamines, antibiotics, antituberculosis agents, cholinergic agents, antimuscarinics, sympathomimetics, sympatholytic agents, autonomic drugs, iron preparations, haemostatics, cardiac drugs, antihypertensive agents, vasodilators, non-steroidal antiinflammatory agents, opiate agonists, anticonvulsants, tranquilizers, stimulants, barbiturates, sedatives, expectorants, antiemetics, gastrointestinal drugs, heavy metal antagonists, antithyroid agents, genitourinary smooth muscle relaxants and vitamins.

4. The sustained release pharmaceutical pellet composition of claim 3 wherein the active ingredient is an opiate agonist selected from the group consisting of the salts of codeine, dextromoramide, hydrocodone, hydromorphine, pethidine, methadone, morphine and propoxyphene.

5. The sustained release pharmaceutical pellet composition of claim 1 wherein the active ingredient has a first dissolution profile measured at a pH of from 1 to 4, and a second dissolution profile measured at a pH of about 7.5 and wherein said first and second dissolution profile are each at least equal to the minimum dissolution required to provide substantially the same bio-availability as with an immediate release oral dosage form.

6. The sustained release pharmaceutical pellet composition of claim 5 wherein the composition, in use, minimizes fluctuations in the plasma concentration of the active ingredient in said patient.

7. The sustained release pharmaceutical pellet composition of claim 1 wherein the coating contains:

as component (a), ethyl cellulose, a quaternary ammonium acrylic or methacrylic polymer, an acrylic or a methacrylic ester copolymer or a mixture thereof;

as component (b), cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, methacrylic acid:acrylic acid ester copolymer, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate and mixtures thereof; and

as component (c), polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol having a molecular weight of from 1700 to 20,000, polyvinyl alcohol and monomers therefor and mixtures thereof.

8. The sustained release pharmaceutical pellet composition of claim 7 wherein the coating comprises:

35 to 75% by weight of component (a);

2-20% by weight of component (b); and

15-40% by weight of component (c).

9. The sustained release pharmaceutical pellet composition of claim 7 wherein the coating also includes up to 50% of plasticizer selected from diethyl phthalate, triethyl citrate, triethyl acetyl citrate, triethyl acetin, tributyl citrate, polyethylene glycol having a molecular weight of from 200 to less than 1700 or glycerol and up to 75% of a filler selected from silicon

dioxide, titanium dioxide, talc, alumina, starch, kaolin, polacrilin potassium, powdered cellulose and microcrystalline cellulose and mixtures thereof, said percentages being based on the total weight of the coating.

10. The sustained release pharmaceutical pellet composition of claim 9 wherein the coating contains:

component (a) 35 to 70%

component (b) 4 to 20%

component (c) 15 to 35%

plasticizer 4 to 30%.

11. A sustained release pharmaceutical pellet composition for administration to a patient at a predetermined dosage and interval which comprises: a core element containing as the active ingredient a therapeutically effective amount of an acid addition salt of morphine and a coating on said core element which comprises the following components:

(a) from 1% to 85% by weight of a matrix polymer which is insoluble at a pH of from 1 to 7.5 and contributes to the control of the rate of release of the active ingredient in the stomach and intestines;

(b) from 1 to 30% of an enteric polymer which is substantially insoluble at a pH of from 1 to 4, sufficient to delay the release of the active ingredient in the stomach, but which is soluble at a pH of from 6 to 7.5 so as not to substantially delay release in the intestines;

(c) from 1 to 60% of a compound soluble at a pH of from 1 to 4, sufficient to enable initiation of release of the active ingredient in the stomach;

said percentages being by weight based on the total weight of components (a), (b), and (c); the ratio of the components (a), (b), and (c) in said coating being such that a dose of the pellet composition delivers to the patient a therapeutically effective amount of said active ingredient over the course of said predetermined interval, so as to maintain an active ingredient blood level at steady state of at least 75% of maximum blood level for more than approximately 4 hours and so that the time at which the active ingredient reaches its maximum concentration is between about 4 and about 30 hours.

12. The sustained release pharmaceutical pellet composition of claim 11 wherein the time at which the active ingredient reaches its maximum concentration is between about 4 and about 12 hours.

13. The sustained release pharmaceutical pellet composition of claim 11 wherein said acid addition salt of morphine is morphine sulphate.

14. The sustained release pharmaceutical pellet composition of claim 11 wherein the composition, in use, minimizes fluctuations in the morphine compound concentration in the plasma of said patient.

15. The sustained release pharmaceutical pellet composition of claim 11 wherein the coating contains:

as component (a), ethyl cellulose, a quaternary ammonium acrylic or methacrylic polymer, an acrylic or a methacrylic ester copolymer or a mixture thereof;

as component (b), cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, methacrylic acid ester copolymer, hydroxypropyl methylcellulose acetate succinate, shellac, cellulose acetate trimellitate and mixtures thereof; and

as component (c), polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol having a molecular weight of from 1700 to 20,000, polyvinyl alcohol and monomers therefore and mixtures thereof.

16. The sustained release pharmaceutical pellet composition of claim 15 wherein the coating comprises:

35 to 75% by weight of component (a);

2-20% by weight of component (b); and

15-40% by weight of component (c).

17. The sustained release pharmaceutical pellet composition of claim 15 wherein the coating comprises:

polyethylene glycol having a molecular weight of from 1700 to 20,000 15 to 40%

ethylcellulose 45 to 65%

methacrylic acid: acrylic

acid ethylester 1:1 copolymer 4 to 20%.

18. A sustained release pharmaceutical pellet composition for administration to a patient at a predetermined dosage and interval which comprises: a core element containing a therapeutically effective amount of at least one active ingredient having an aqueous solubility of at least 1 in 30 and a coating on said core element which comprises the following components:

(a) at least 35% by weight of a matrix polymer which is insoluble at a pH of from 1 to 7.5 and is composed of ethyl cellulose, a quaternary ammonium acrylic or methacrylic polymer, an acrylic or a methacrylic ester copolymer or a mixture thereof which contributes to the control of the release of the active ingredient in the stomach and intestines;

(b) from 1 to 30% of an enteric polymer which is substantially insoluble at a pH of from 1 to 4, sufficient to delay the release of the active ingredient in the stomach, but which is soluble at a pH of from 6 to 7.5 so as not to substantially delay release in the intestines;

(c) from 1 to 60% of a compound soluble at a pH of from 1 to 4, sufficient to enable initiation of release of the active ingredient in the stomach; said percentages being by weight based on the total weight of components (a), (b), and (c); the ratio of the components (a), (b), and (c) in said coating being such that a dose of the pellet composition delivers to the patient a

therapeutically effective amount of said active ingredient over the course of said predetermined interval, so as to maintain an active ingredient blood level at steady state of at least 75% of maximum blood level for more than approximately 4 hours and so that the time at which the active ingredient reaches its maximum concentration is between about 4 and about 30 hours.

19. The sustained release pharmaceutical pellet composition of claim 18 wherein the time at which the active ingredient reaches its maximum concentration is between about 4 and about 12 hours.

20. A sustained release pharmaceutical pellet composition for administration to a patient at a predetermined dosage and interval which comprises: a core element containing as the active ingredient a therapeutically effective amount of an acid addition salt of morphine and a coating on said core element which comprises the following components:

(a) at least 35% by weight of a matrix polymer which is insoluble at a pH of from 1 to 7.5 and is composed of ethyl cellulose, a quaternary ammonium acrylic or methacrylic polymer, an acrylic or a methacrylic ester copolymer or a mixture thereof which contributes to the control of the release of the active ingredient in the stomach and intestines;

(b) from 1 to 30% of an enteric polymer which is substantially insoluble at a pH of from 1 to 4, sufficient to delay the release of the active ingredient in the stomach, but which is soluble at a pH of from 6 to 7.5 so as not to substantially delay release in the intestines;

(c) from 1 to 60% of a compound soluble at a pH of from 1 to 4, sufficient to enable initiation of release of the active ingredient in the stomach; said percentages being by weight based on the total weight of components (a), (b), and (c); the ratio of the components (a), (b), and (c) in said coating being such that a dose of the pellet composition delivers to the patient a therapeutically effective amount of said active ingredient over the course of said predetermined interval, so as to maintain an active ingredient blood level at steady state of at least 75% of maximum blood level for more than approximately 4 hours and so that the time at which the active ingredient reaches its maximum concentration is between about 4 and about 30 hours.

21. The sustained release pharmaceutical pellet composition of claim 20 wherein the time at which the active ingredient reaches its maximum concentration is between about 4 and about 12 hours.

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